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No. 93-1385

IN THE

SUPREME COURT OF THE UNITED STATES

OCTOBER TERM, 1993

NORTH AMERICAN VACCINE, INC. and
NATIONAL RESEARCH COUNCIL OF CANADA,
Petitioners,

v.

AMERICAN CYANAMID COMPANY and
PRAXIS BIOLOGICS, INC.,
Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO
THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

RESPONDENTS' BRIEF IN OPPOSITION

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COUNTER-STATEMENT OF THE QUESTION PRESENTED

Whether the U.S. Court of Appeals for the Federal Circuit properly affirmed a judgment of noninfringement based on an issue of claim interpretation, after ruling that the district court erred in relying on certain evidence, where:

(a) petitioners asked the Federal Circuit to review the district court's claim interpretation *de novo* and to construe the claims as a matter of law,

(b) the Federal Circuit relied upon undisputed facts and conclusions of law to interpret the claims, and

(c) the district court almost certainly would have reached the same claim interpretation even without the alleged error.

STATEMENT PURSUANT TO RULE 29.1

The parents, subsidiaries and affiliates of Respondents American Cyanamid Company and Praxis Biologics, Inc., other than those that are wholly owned, are listed below:

AC Molding Compounds

American Melamine Industries (a partnership)

Biotechnology Research and Development Corporation
(Consortium consisting of the following companies owning 400 shares of common stock:
Agricultural Research and Development Corp.
American Cyanamid Company
Amoco Technology Company
Imcera Group, Inc.
Dow Elanco
Hewlett-Packard Company
Ecogen, Inc.)

B. Braun-Dexon GmbH

B. Braun Melsungen AG)

B. Braun-Dexon (Portugal) Produtos Hospitalares Limitada

B. Braun-Dexon, S.A.

Criterion Catalyst Canada Inc.

Criterion Catalyst Company

Criterion Catalyst Company L.P. (a limited partnership)

Cyanamid India Limited

Cyanamid Italia S.p.A.

Cyanamid (Pakistan) Limited

Cyanamid Taiwan Corporation

CYRO Canada Inc.

CYRO Industries (a Partnership)

Dyno Cyanamid B.V.

Dyno Cyanamid C.V.

Dyno Cyanamid K.S.

Esterfarm Laboratori Farmaceutici S.r.l.

Eximp, S.A.

Irbi, S.p.A.

Laboratorios Sobrino S.A.

Laminate Industries (Proprietary) Limited

Lederle (Japan), Ltd.

Lederle (Nigeria) Limited

Mitsui-Cyanamid, Ltd.

Productora-Distribuidora Sobrino, S.A.

Sutumex, S.A. de C.V.

Suzhou Lederle Pharmaceutical Company Ltd.

Takeda Italia Farmaceutici S.p.A.

YuHan-Cyanamid, Inc.

Miscellaneous Minor Equity Investments:

Company

American Casualty Excess Insurance Company, Ltd.

Applied Microbiology Inc.

California Laboratories Inc.

Corporate Officers and Directors Assurance, Ltd. (CODA)

Cortecs Limited

Credence Investment and Finance Pvt. Ltd.

Cyanotech Corporation

Dallas Investment and Trading Co. Pvt. Ltd.

Delta Holdings, Inc.

Ecogen Inc.

Embrex Inc.

EXEL Limited

Hopewell International Insurance Limited

ImClone Systems, Inc.

Inmunologia Y Genetica Aplicada, S.A.

Ingenasa

IRE Celltarg

MGI Pharma, Inc.

Molecular Genetics, Inc.

Quadra Logic Technologies, Inc.

Senorita Investment and Trading Co. Pvt. Ltd.

Sepracor, Inc.

Societe Exploitation et Recherche Chirurgicales Lederle

Techniclone International Corp.

United Insurance Company

Uresil, L.P. (a partnership)

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RESPONDENTS' BRIEF IN OPPOSITION

COUNTER-STATEMENT OF THE CASE

Introduction

In this patent infringement action, tried to the bench, the dispositive issue involved interpreting the meaning of claim language. Petitioners allege that the Federal Circuit improperly affirmed the judgment because, in the course of interpreting the claims, it ruled that the district court should not have relied on certain evidence. Before the Federal Circuit, however, petitioners argued that claim interpretation in this case was an "issue of law" for the

court to decide "*de novo.*" Having urged that position before the Federal Circuit, petitioners are estopped from reversing positions now and arguing that the Federal Circuit erred by interpreting the claims itself rather than remanding to the district court.

Moreover, when interpreting the claims, the Federal Circuit did not engage in fact finding. The Federal Circuit concluded that the claims could be interpreted by relying on the claim language and the descriptions in the patent. Petitioners' testimonial evidence for an expansive interpretation, testimony that the Federal Circuit rejected on legal grounds, did not raise disputed factual issues requiring remand.

Furthermore, after reviewing the evidence, the Federal Circuit properly concluded that the district court's alleged error was "harmless." Petitioners attempt to convince this Court otherwise by misrepresenting the district court's reliance on the alleged error and by citing to the district court's courteous but perfunctory remarks at the beginning of its opinion that the case was "a close one." A careful review of the trial evidence, the district court opinion, and the Federal Circuit opinion, however, reveals that the district court almost certainly would have reached the same claim interpretation even without the alleged error. Thus, the alleged error did not "substantially influence" the district court and certainly does not warrant expending further judicial resources on either this petition or a remand.

In any event, this case raises only issues peculiar to its own facts and proceedings. Thus, this case does not warrant a writ of certiorari.

The Patent in Suit

The patent in suit covers certain "conjugate" vaccines, which are made of billions of polysaccharide molecules, each of which is linked to a protein. In essence, the patented invention covers a product made by a two-step process to link protein to the polysaccharide, which would not occur naturally. First, the polysaccharide must be treated to create a reactive site (called "an aldehyde group") at a terminal location, i.e., at the end of the polysaccharide. Second, the activated polysaccharide is chemically combined with a selected protein. In the resulting conjugate, only one protein is linked to a polysaccharide and crosslinking, which is defined as two or more proteins linked by a polysaccharide, is thus avoided.

Petitioners, the patent owner and exclusive licensee, asserted claims 12 and 25 of their patent against respondents. Both of the asserted claims are dependent upon claim 11, which reads:

> 11. An antigenic-polysaccharide:protein conjugate wherein the polysaccharide and protein are covalently linked through a
>
> $$-CH_2-\overset{H}{N}-\text{protein}$$
>
> linkage to a terminal portion of the polysaccharide without significant cross-linking, said antigenic polysaccharide having a [molecular weight] above about 2000.

The infringement issue raised by this petition focused upon the meaning of the phrase "linkage to a terminal portion of the polysaccharide without significant crosslinking" in claim 11.

The "summary of the invention" in the patent begins by describing the formation of the protein linkage to a terminal portion of the polysaccharide as follows:

> We have found it possible to introduce a free aldehyde group into the polysaccharide molecule in a terminal location and to specifically couple this aldehyde group to protein without activating other functional groups on the polysaccharide.

(2a, col. 2, lines 33-37).[1] This sentence refers to the protein linkage in singular terms, using the phrases "a free aldehyde group," "this aldehyde group," and "in a terminal location."

Throughout its text, the patent refers to the linkage between the protein and polysaccharide in singular terms. At no point does the patent teach that the inventors contemplated creating more than one reactive site on the polysaccharide (such as by use of the phrase "at least one") or linking the polysaccharide to more than one protein. When describing other aspects of their invention, however, the inventors used the conventional phrase "at least one" when they contemplated more than one (*see, e.g.*, 5a-6a, claims 22, 23 and 25).

The patent teaches that crosslinking (as would occur with polysaccharides having two or more active sites)[2] is a structural characteristic to be avoided (*see, e.g.*, 2a-3a,

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[1] Citations preceded by "Pet. at _a," are to the Appendix to the Petition for a Writ of Certiorari; citations preceded by the letter designation "_a" are to the appendix to the Respondents' Brief in Opposition.

[2] Polysaccharides activated at one end are sometimes referred to as "monofunctional." Polysaccharides activiated at both ends are sometimes referred to as a "difunctional." Polysaccharides having more than two reactive sites are sometimes referred to as "polyfunctional."

col. 2, lines 37-39 and 62-63; 5a, col. 3, lines 62-63). Nowhere in the specification is crosslinking of any type identified as a desirable, or even an acceptable, aspect of the invention. Crosslinking is prevented by a single terminal linkage, i.e., monofunctionality.

No vaccine produced in accordance with petitioners' patent has been approved for sale in either the United States or abroad (18a-20a).

HibTITER

The accused product, HibTITER, is a vaccine against *Haemophilus influenza* type b ("Hib") bacteria, one of the leading causes of childhood meningitis. HibTITER was developed independently of petitioners' patent by Praxis Biologics, a subsidiary of American Cyanamid (21a-23a). HibTITER was the first vaccine against Hib bacteria approved by the FDA for use in young children (24a). Since HibTITER's approval, vaccinating children against Hib bacteria has become standard pediatric practice, and the incidence of meningitis caused by Hib bacteria has declined markedly (24a-25a).

HibTITER is made by linking proteins to difunctional Hib polysaccharide (fragments having reactive sites at each end of the fragment) (25a-26a). Because the Hib polysaccharide fragments have two reactive sites, each can link to a different protein, thereby producing crosslinked conjugates (27a-28a).

The Trial

From the outset of the trial, petitioners avoided the actual words of the patent and introduced new and

broader terms. For example, petitioners urged in their opening statement:

> [T]he '170 patent solves [the problem] by just making polysaccharide chains which have free aldehyde groups, single terminal aldehyde groups on one end or on both ends . . . .

(7a). Nowhere did the patent state that aldehyde groups could be formed "on one or both ends" of the polysaccharide.

Petitioners, however, urged that their expansive interpretation of the claims followed from the patent's "summary of the invention," the experiments reported in the patent, and the mention of *Haemophilus influenza* polysaccharide in claim 12. As a result, much of the trial focused upon whether these disclosures supported petitioners' argument. Petitioners' evidence in support of their argument consisted of the testimony of Dr. Harold Jennings, one of the inventors, and Dr. Gary Schoolnik, a retained expert witness.

Dr. Jennings testified what he "intended" the patent disclosure and claims to mean. Dr. Jennings testified that he intended the language "linkage to a terminal portion of the polysaccharide" to include protein linkages at both ends of the polysaccharide, contending "this can be read from the difference between my publications and . . . the patent, in which we do allow for crosslinking" (17a). Dr. Jennings testified also that he did not intend the "summary of the invention" or the description of his experiments in his patent to suggest that his invention was limited to linkages at a single terminal portion of the polysaccharide (16a-17a).

On cross-examination, respondents challenged Dr. Jennings's self-serving characterization of his patent, using

in part a 1980 NIH speech and 1981 article authored by Dr. Jennings which reported on the same experiments described in the patent (20a). Indeed, Dr. Jennings gave the 1981 article to his attorney, who used the article as a basis for drafting the patent (14a). Both refuted Dr. Jennings's direct testimony that it was a matter of indifference to him in his patent whether protein linked to one or both ends of the polysaccharide. Thus, respondents used the speech and article to rebut Dr. Jennings's after-the-fact characterization of his patent and his statements as to his intended meaning.

Dr. Schoolnik's testimony centered on the patent's mention of *Haemophilus influenza*, along with several other types of polysaccharides, in claim 12. Petitioners argued this reference to *Haemophilus influenza* meant the claims must cover linkages to both terminal portions of the polysaccharide. Dr. Schoolnik conceded that "my entire interpretation of the language where it is singular is driven by the specific examples of polysaccharides in claim 12 . . . ." (12a-14a).

However, on cross-examination, Dr. Schoolnik admitted that a number of other polysaccharides in claim 12 were polyfunctional and would form multiple linkages along the backbone of the polysaccharide. Dr. Schoolnik further admitted that such polysaccharides would not fall within the language of claim 11 (11a-12a). Thus, Dr. Schoolnik's position was reduced to an argument that one polysaccharide mentioned in claim 12 (*Haemophilus influenza*) should be used to construe the meaning of claim 11, while other polysaccharides mentioned in claim 12 should be ignored (8a-10a). Dr. Schoolnik could offer no explanation as to why *Haemophilus influenza* should be singled out of claim 12, rationalizing only

that "I'm not that concerned about the other polysaccharides [in claim 12]" (8a-9a).

The District Court Opinion

Following closing arguments, the district court dictated a 26-page opinion.

At the outset, the court complemented counsel for their trial presentation and politely remarked that the "case is a close one." The court then proceeded to reject every shred of evidence offered by petitioners as demonstrating a broader than normal meaning of the disputed claim language. At no point in the opinion did the court again suggest that the case was "close." Indeed, the court did not even consider it necessary to rely on respondents' affirmative evidence on the issue of claim interpretation.

The court began its analysis of the phrase "a terminal portion of the polysaccharide without significant cross-linking" by focusing on the language itself, explaining that "[t]he phrase 'a terminal portion' is, of course, in the singular." (Pet. at 31a). The court noted that petitioners wished to interpret the language to mean "a terminal portion of the polysaccharide at one or both ends," while respondents urged that the claim language "means what it says, and refers only to a single terminal portion." (Pet. at 34a).

The court then proceeded to assess petitioners' argument that the phrase should be interpreted differently than its ordinary meaning. The court set the framework for this inquiry as follows:

> [W]e need to look at some of the other evidence that can be considered properly under the law on the question of interpretation. We, of course, need to look at the other portions of the patent:

> the summary of the invention; the description of the experiments, other claims besides 11, 12 and 25. In other words, the whole patent.

(Pet. at 34a). Thus, the district court focused on the disclosures in the patent, especially the "summary of the invention" and the experiments. The court also considered the testimony of Dr. Jennings and Dr. Schoolnik.

The district court viewed "the most important point in the evidence" to be that "the laboratory work carried out by Dr. Jennings leading up to the patent was specifically designed to produce polysaccharides with protein linkage at only one end of the polysaccharide." (Pet. at 35a). The court noted that Dr. Jennings "conducted experiments with the desire and purpose of producing monofunctionality, that is, linkage at one terminal portion." *Id.*

The court rejected Dr. Jennings's testimony that "when it came to taking out his patent, he intended to claim something broader than what he talked about in his speech and his article," finding instead that "the descriptions which develop the concept of monofunctionality are carried over into the patent." (Pet. at 37a-38a). In particular, the court pointed to the patent's "summary of the invention," which employed wording "very, very close to the wording in [the 1981] article . . . which was obviously designed in the article to convey and elaborate upon the monofunctional approach." (Pet. at 38a). The court also found that "anyone reading the patent will find over and over again references which talk about the single terminal group." *Id.*

The court also rejected Dr. Jennings's testimony that the differences between his patent and his speech and article showed his intention to cover protein linkages

at both terminal ends of the polysaccharide (which results in crosslinking). The court found instead that:

> [T]here is nothing in this patent affirmatively teaching anything about achieving cross-linking. There is nothing in the patent except a negative view of cross-linking.

(Pet. at 40a). Thus, the court concluded that if Dr. Jennings intended to cover linkages at both terminal portions, "something that can be easily expressed in the English language," "[h]e did not express it." The court went on to explain:

> And that is the basic reason why I am holding in favor of the defendants on the question of interpretation. There are ample means through simple devices of wording to convey what he claims was his intention. He simply did not do it.

(Pet. at 39a).

In addition, the court rejected the testimony of Dr. Schoolnik for two independent reasons. First, Dr. Schoolnik's interpretation, focusing on the mention of *Haemophilus influenza* in claim 12, conflicted with the experiments and theory set forth in the patent. As the court explained:

> To allow all of that weight, really massive weight of discussion, descriptions of experiments and so forth, to be cancelled out by the two words "*Haemophilus influenza,*" in my mind, would not be a fair method of interpretation.

(Pet. at 41a). Second, the court recognized the illogic of Dr. Schoolnik's testimony that the mention of *Haemophilus influenza* in claim 12 "drives the interpretation of the entire patent" but the mention of polyfunctional polysaccharides in that same claim should be ignored

(Pet. at 40a). The court concluded that it would be "improper to ignore [the main teaching of the patent] in respect of *Haemophilus influenza* any more than for the [types of bacteria] where polyfunctionality occurs." (Pet. at 42a).

Thus, the district court concluded that the asserted claims were limited to conjugate vaccines with protein linked at one terminal portion of the polysaccharide. Since it was undisputed that a high proportion of Hib-TITER comprised conjugates with protein linked at both ends of the polysaccharide (i.e., were crosslinked), the court found no infringement and entered judgment for respondents.

The Appeal

On appeal, petitioners urged that claim construction in this case "is an issue of law freely reviewable on appeal" (29a). Respondents disagreed, but the Federal Circuit sided with petitioners and concluded that, under the particular facts of this case, claim interpretation "is a matter of law for this court to decide without special deference to the district court." (Pet. at 7a).

The Federal Circuit then began its analysis, as did the district court, "with the language of the claims themselves." (Pet. at 7a). The Federal Circuit focused first on the language "a terminal portion," noting that the claim could have used language expressly covering more than one terminal portion, and then looked to the patent for any indication "that the inventors here intended it to have other than its normal singular meaning." *Id.*

Like the district court, the Federal Circuit found no indication in the patent that the inventors intended to include crosslinking within the scope of their invention

(Pet. at 8a). To the contrary, the Federal Circuit observed that "[a]ll references to polysaccharide linkages speak of a linkage, not multiple linkages." *Id.* As one example, the Federal Circuit cited the same sentence from the patent's "summary of the invention" that the district court had cited and which appeared virtually verbatim in Dr. Jennings's article. *Id.*

The Federal Circuit also focused on Dr. Jennings's experiments reported in the examples of the patent, noting that these experiments also described the linkage in singular terms. In addition, the court cited one experiment where the conditions chosen were described as "unlikely" to produce linkage at both terminals. (Pet. at 9a). Thus, the Federal Circuit concluded that "[t]he examples in the [patent] specification also support linkage at only one terminal." (Pet. at 8a).

The Federal Circuit also addressed Dr. Jennings's testimony that he intended to include linkages at both ends of the polysaccharide within the scope of his invention. The Federal Circuit first explained that "[a] patent applicant cannot disclose and claim an invention narrowly and then, in the course of an infringement suit, argue effectively that the claims should be construed to cover that which is neither described nor enabled in the patent." (Pet. at 10a). The Federal Circuit then went on to rule Dr. Jennings's "after-the-fact testimony is of little weight compared to the clear import of the patent disclosure itself." *Id.*

As to Dr. Schoolnik's argument that the mention of *Haemophilus influenza* polysaccharide in claim 12 mandated an expansive interpretation of claim 11, the Federal Circuit rejected this contention on three grounds. First, it noted that dependent claims "are only an aid to

interpretation and are not conclusive" and could not dictate the interpretation of claim 11 in the absence of further disclosure of difunctional molecules in the patent (Pet. at 11a). Second, the Federal Circuit cited testimony from one of respondents' experts, Dr. Ronald Eby, that *Haemophilus influenza* could be treated to create a protein linkage at only one terminal portion of the polysaccharide. *Id.* Third, like the district court, it concluded that the interpretation of "linkage to a terminal portion" could not be dictated by claim 12 because polyfunctional polysaccharides, which petitioners conceded are not within the scope of the claimed invention, are also recited in claim 12. *Id.*

The Federal Circuit then commented on the district court's reliance on Dr. Jennings's speech and article. Apparently concerned that the district court had used the speech and article to interpret the claims rather than as an aid to understanding what was written in the patent and the testimony at trial (a concern that respondents believe was unwarranted), the Federal Circuit commented that "[a] patent is to be interpreted by what it states rather than by what the inventor wrote in a scientific publication." (Pet. at 13a). The Federal Circuit went to conclude that "it was error, albeit harmless error, for the district court to conclude that the narrow scope of the article limits the scope of the patent claims, which should be judged on their own merits." *Id.*

On the basis of the foregoing analysis, the Federal Circuit affirmed the district court's holding of noninfringement.

REASONS FOR DENYING THE WRIT

Petitioners' request for review by writ of certiorari of the Federal Circuit's decision should be denied because none of the requisite special and important reasons for review by this Court is presented. The Federal Circuit's decision raises none of the consideration set forth in Rule 10 of the rules of this Court. Moreover, several additional considerations, argued below, confirm that the petition should not be granted.

I.
PETITIONERS ARE ESTOPPED FROM ARGUING THAT THE FEDERAL CIRCUIT IMPROPERLY DECIDED CLAIM INTERPRETATION AS A MATTER OF LAW.

Before this Court, petitioners argue that the Federal Circuit "erred by deciding factual questions in interpreting the claims of the patent" and "intruded upon the assigned role of the District Court." Before the Federal Circuit, however, petitioners argued that claim interpretation in this case raised only "an issue of law" and asked the court to review the district court's claim construction "*de novo.*" Thus, if the Federal Circuit erred, petitioners, having invited the error, are estopped from asking this Court to review the Federal Circuit's interpretation of the claims.

At every opportunity before the Federal Circuit, petitioners argued that the claims should be interpreted as a matter of law. In their principal brief on appeal, petitioners argued "[c]laim construction is an issue of law freely reviewable on appeal" (29a). In their reply brief, petitioners argued "this appeal . . . raises only questions of law and does not involve disturbing any of the district court's underlying factual determinations" (30a). During

oral argument, and in response to questioning from the Federal Circuit panel as to whether the claim construction issue raised a question of law or fact, petitioners' counsel stated:

> We are not contesting any of the District Court's findings about any of those terms . . . the question before this Court is one of claim construction that should be reviewed *de novo,* Your Honor.

(32a).

The Federal Circuit adopted petitioners' argument, holding that resolution of the disputed issues "regarding the meaning of contested language . . . is a matter of law for this court to decide without special deference to the district court." (Pet. at 7a). The Federal Circuit proceeded to interpret the claims, committing what petitioners now allege to be error.

Having repeatedly invited the Federal Circuit to construe the claims "as a matter of law," petitioners complain now that the Federal Circuit erred by doing just that. A party cannot appeal, however, from an alleged error induced by its own action. *See, e.g., F.W. Woolworth Co. v. Contemporary Arts, Inc.,* 344 U.S. 228, 231 (1952) (no right to complain of exclusion of evidence in response to petitioner's own objections); *Perego v. Dodge,* 163 U.S. 160, 164-65 (1896) (no right to complain that a complaint in equity should have been dismissed because of an adequate remedy at law when the petitioner voluntarily invoked equity jurisdiction); *St. Louis Public Schools v. Risley,* 77 U.S. 91 (1870) (no right to predicate error on instructions given at petitioner's own request). Moreover, after waiving a position before the Court of Appeals, an appellant cannot resurrect that position before this Court. *See Helvering v.*

Wood, 309 U.S. 344, 349 (1940) (petitioner not permitted to raise an issue which he had expressly waived in his brief before the Circuit Court of Appeals).

Thus, in view of their argument urged upon and adopted by the Federal Circuit, petitioners are estopped from reversing their position and arguing now that the Federal Circuit erred by interpreting the claims as a matter of law.

II.
THE FEDERAL CIRCUIT DID NOT ENGAGE IN FACT FINDING.

The Federal Circuit did not "improperly [decide] the disputed facts underlying the interpretation of the patent claims" as petitioners allege. The Federal Circuit's opinion is premised upon the language of the claims and the disclosure in the patent. Beyond that, the Federal Circuit rejected petitioners' testimonial evidence on legal grounds. Thus, the Federal Circuit properly interpreted the claims as a matter of law.

Like the district court, the starting point for the Federal Circuit's analysis was the claim language. The Federal Circuit properly viewed itself as capable of understanding the English language. In so doing, the Federal Circuit agreed with the district court's understanding that the language "a terminal portion," standing alone, means a single terminal portion.

The Federal Circuit then looked to the disclosures in the patent, finding many references to linkages to a single terminal portion of the polysaccharide, no affirmative teaching of linking protein to both terminal portions of the polysaccharide, and a clear teaching away from cross-linking. Thus, like the district court, the Federal Circuit

concluded that the description of the invention in the patent suggested that the scope was limited to conjugates with protein linked to a single terminal portion of the polysaccharides.

The Federal Circuit then addressed petitioners' arguments in favor of a more expansive interpretation of the claims – Dr. Jennings's testimony as to his intended meaning of the patent's disclosure and claims, and Dr. Schoolnik's testimony as to the import of claim 12 mentioning *Haemophilus influenza* polysaccharide. The Federal Circuit rejected Dr. Jennings's testimony on legal grounds – intent of the inventor is irrelevant to claim interpretation. The Federal Circuit then rejected Dr. Schoolnik's testimony on multiple grounds, including his inability to explain why mention of *Haemophilus influenza* polysaccharide in claim 12 should mandate the interpretation of claim 11 while other polysaccharides should be ignored. The district court rejected Dr. Schoolnik's testimony for similar reasons.

Thus, the second reason given by the Federal Circuit for rejecting Dr. Schoolnik's testimony, the testimony by Dr. Eby establishing that Hib polysaccharide can be pretreated such that protein will link to only one terminal portion of the polysaccharide, was unnecessary to its analysis. Petitioners misrepresent the record, however, when they argue that the Federal Circuit relied on testimony that "contradicts a finding of the District Court" and assert that "[t]he District Court specifically stated that it would not rely upon the testimony of this witness in interpreting the patent . . . ." (Pet. at 12). Dr. Eby's testimony was fully consistent with the district court's opinion. Indeed, the district court cited a related stipulation that "on some of these [types of bacteria] which would not naturally and easily yield the monofunctional

result, such a result could be obtained if there was pretreatment of the kind taught at an earlier point in the patent." (Pet. at 41a). Moreover, the district court never suggested that it would not rely on any of Dr. Eby's testimony, only that it would not rely on Dr. Eby's "opinion on interpretation" (28a).

In short, following the Federal Circuit's analysis, no outstanding factual disputes remained to be tried. As a result, the Federal Circuit properly construed the claims as a matter of law.

III.
THE DISTRICT COURT'S JUDGMENT WAS NOT SUBSTANTIALLY INFLUENCED BY THE ALLEGED ERROR.

The district court's judgment was not "substantially influenced" by the alleged error. With or without Dr. Jennings's speech and article, the district court almost certainly would have adopted the same claim interpretation.

A careful review of the district court opinion reveals that the district court reached its claim interpretation principally because (1) the phrase "linkage to a terminal portion of the polysaccharide" ordinarily would be viewed as meaning a single linkage ("[t]he phrase 'a terminal [portion]', of course, is in the singular" Pet. at 38a); (2) the patent described the linkage only in singular terms ("anyone reading the patent will find over and over again references which talk about the single terminal group," *Id.*); and (3) the patent described only the absence of crosslinking ("[t]here is nothing in the patent except a negative view of crosslinking," Pet. at 40a). The speech and article had little bearing on any of these three elements of the district court's analysis.

Thus, contrary to petitioners' allegations, the article and speech were not "the basic reason" the district court ruled in favor of respondents or "the most important point in the evidence" for the district court. (See Pet. at 8). The "basic reason" given by the district court for ruling in defendant's favor was:

> There are ample means through simple devices of wording to convey what [Dr. Jennings] claims was his intention. He simply did not do it.

(Pet. at 39a). In other words, the patent disclosed no support for petitioners' claim interpretation. Furthermore, the "most important point in the evidence" was Dr. Jennings's monofunctional objective in "the laboratory work . . . leading up to the patent." (Pet. at 35a). That objective was manifested throughout the patent itself, especially in the examples of the patent which described exactly the same experiments that had been reported earlier in the speech and article.

The district court used the speech and article principally to evaluate Dr. Jennings's testimony that he "intended" his invention to cover protein linkages at both ends of the polysaccharide and that he "expressed" that intention in the patent. The district court disagreed, recognizing that the patent described the same experiments and used the same language appearing in Dr. Jennings's speech and article, which Dr. Jennings unequivocally admitted were directed toward a monofunctional approach. Thus, the district court used the speech and article for what respondents believe was an entirely proper purpose – to help it understand the *disclosures* in the patent, not as a basis for construing the *claims* per se as the Federal Circuit seemed to suggest.

Even if the district court's reliance on Dr. Jennings's speech and article was error, however, its judgment was not swayed by the error. As noted above, the district court relied principally upon the claim language and the patent disclosure, both of which the district court viewed, standing alone, as supporting the claim interpretation adopted. Beyond that, the district court addressed the testimony of Dr. Jennings and Dr. Schoolnik that the claim should be interpreted more broadly, neither of which would have been bolstered by ignoring the speech and article.

Dr. Jennings's testimony was impeached by the speech and article, but the Federal Circuit ruled that Dr. Jennings's testimony was "of little weight" in any event, a ruling not challenged by petitioners. Thus, his testimony cannot be grounds for concluding that the district court might have reached a different result without the speech and article. Indeed, without his testimony, there would have been little need for the district court to rely on the speech and article.

The district court's rejection of Dr. Schoolnik's testimony was not dependent upon the speech and article. Dr. Schoolnik's testimony centered on his argument that the interpretation of the patent should be driven by the mention of *Haemophilus influenza* polysaccharide in claim 12. The district court rejected this testimony, however, because Dr. Schoolnik could offer no explanation as to why the Hib polysaccharide should dictate the meaning of claim 11 while other polysaccharides, incompatible with his claim interpretation, should be ignored. This analysis of his testimony was completely unrelated to the district court's consideration of Dr. Jennings's speech and article.

Thus, even without the speech and article, there can be little doubt that the district court would have reached the same conclusion. Notwithstanding the district court's polite remarks at the beginning of its opinion, this was not a "close" case. Given the district court's analysis and the Federal Circuit's ruling regarding the testimony of Dr. Jennings, virtually no record evidence supports petitioners' strained interpretation of the claims.

In short, this is a case like *United States v. Borden Co.*, 347 U.S. 514 (1954), a Sherman Act case where this Court, after considering the record and the offers of proof, held that certain evidentiary rulings, even if error, were harmless, explaining:

> it does not appear that admission of the evidence in question would have been sufficient to change the conclusion that the Government had not established a case under the Sherman Act; hence the rulings cannot be said to have affected substantial rights of the parties within the meaning of 28 U.S.C. §2111.

Id. at 516. Similarly here, because it is unlikely that the Federal Circuit's evidentiary ruling would have changed the district court's interpretation of the claim language, the district court's reliance on that evidence did not affect the substantial rights of petitioners within the meaning of 28 U.S.C. §2111. Thus, the Federal Circuit properly affirmed the district court judgment.

Finally, the application of the harmless error doctrine was peculiar to the facts and proceedings in this case. Consequently, the Supreme Court's review of this case would be of little value to future cases. As this Court observed in *Kotteakos v. United States*, 328 U.S. 750 (1946):

> In the final analysis judgment in each case must be influenced by conviction resulting from examina-

> tion of the proceedings in their entirety, tempered but not governed in any rigid sense of stare decisis by what has been done in similar situations.

Id. at 762. Thus, this petition does not warrant certiorari.

CONCLUSION

For the foregoing reasons, the petition for a writ of certiorari should be denied.

Respectfully submitted,

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APPENDIX A – United States Patent 4,356,170
columns 2, 3 and 10

IMMUMNOGENIC POLYSACCHARIDE-PROTEIN CONJUGATES

Salmonella O-antigens: preparation of an octasaccharide-bovine serum albumin immunogen representative of Salmonella sero-group B O-antigen and characterization of the antibody response", J. of Immunol. 120, 1750, 1978. References (4), (5) and (7) used water-soluble carbodiimide reagents and formed amido linkages to the protein. Reference (6) carried out a more complex procedure including activation of the polysaccharide with cynaogen bromide, first conjugation of the protein with adipic hydrazide, then treating the mixture with a water-soluble carbodiimide; to form an amido type linkage to the protein and a complex variety of linkages from the adipic spacer to the polysaccharide. These previous methods either (a) utilized many randomly activated functional groups (hydroxyl or carboxylate) on the various polysaccharides leading to considerable crosslinking and poorly defined, low solubility conjugates; (b) required a specific functionality of limited applicability; (c) resulted in less incorporation of polysaccharide than was desired; or (d) led to extraneous modification of the polysaccharide which would alter its antigenicity.

Relatively small disaccharides have been conjugated to protein via their terminal hemiacetal groups using sodium cyanoborohydride reagent. See: (8) B. A.

Schwartz and G.R. Gray, Arch. Biochem. Biophys. 181, 542-49, 1977. When we attempted to apply this technique to the high molecular weight meningococcal polysaccharides, unsatisfactory incorporation resulted.

SUMMARY OF THE INVENTION

We have found it possible to introduce a free aldehyde group into the polysaccharide molecule in a terminal location and to specifically couple this aldehyde group to protein without activating other functional groups on the polysaccharide. This procedure avoids crosslinking and extraneous chemical modification of the bulk of the polysaccharide resulting in better defined immunogens.

This invention includes a method of preparing antigenic polysaccharide: Protein conjugates, comprising:

(a) providing an antigenic polysaccharide which has reactive vicinal hydroxyl groups in a terminal portion of the molecule;

(b) subjecting said vicinal hydroxyl groups at a terminal location to controlled oxidation to generate a reactive aldehyde group therefrom on the polysaccharide;

(c) selecting a physiologically tolerated protein having a free amino group and reacting said amino group with said aldehyde group by reductive amination, to covalently link said polysaccharide and protein; and

(d) recovering a substantially non-crosslinked, soluble, antigenic polysaccharide:protein conjugate.

Another part of the invention is the antigenic-polysaccharide:protein conjugate wherein the polysaccharide and protein are covalently linked through a

$$-CH_2-\underset{\text{H}}{N}-\text{protein}$$

linkage to a terminal portion of the polysaccharide without significant cross-linking, said antigenic polysaccharide having a MW above about 2000.

The invention further includes a vaccine comprising at least one of said conjugates, particularly a vaccine for human infants, and a method of immunizing with said vaccines.

DETAILED DESCRIPTION

Various antigenic polysaccharides may be used according to this invention, the only requirement being that they contain vicinal hydroxyl groups in a terminal portion of the molecule. In particular, capsular polysaccharides from bacteria are most suitable for vaccine purposes. In some cases, unlinked terminal non-reducing sialic acid residues are present in the polysaccharide and they contain suitable vicinal hydroxyl groups. Polysaccharides which initially have a terminal reducing sugar residue can be subjected to a controlled reduction to generate reactive vicinal hydroxyl groups from this terminal residue. One particular example of such a reducing sugar residue is the N-acetylmannosamine residue. Other samples of such residues include those of glucose, glucosamine, rhamnose, and ribose. Antigenic polysaccharides which are particularly useful include those derived from meningococci, *Haemophilus influenza,* pneumococci, *B*-hemolytic streptococci and *Escherichia coli.* The polysaccharide MW suitably is within about 2,000-100,000 for best coupling and antigenicity.

The reduction of the terminal reducing sugar residues is suitably effected using a mild reducing agent, e.g.

sodium borohydride or its equivalent at a pH of about 7.5 to 10. Preferably $NaBH_4$ is used at a pH of 8-9 to minimize side reactions.

It has been found possible to selectively oxidize the terminal vicinal hydroxyl groups to form a terminal aldehyde group by controlled oxidation. This oxidation may be effected conveniently with periodate reagent for a limited time. For instance, approximately 10 mg of polysaccharide suitably is oxidized with about 1 ml of approximately 100 mM sodium metaperiodate solution for about 10-15 min. at room temperature. The reaction time can be varied to accomodate other amounts of periodate to obtain equivalent oxidation. The vicinal hydroxyl groups are cleaved to leave the terminal —CHO group on the polysaccharide.

The protein component may be any physiologically tolerated protein having a free amino group. Preferably, the protein is itself an immunogen. Suitable proteins include tetanus toxoid, diphtheria toxoid and other proteins derived from vacteria. It is possible that other proteins containing lysine residues, e.g. a synthetic polylysine may be useful in a particular system. The bacterial source may be, e.g. *B*-hemolytic streptococci, *Haemophilus influenza,* meningococci, pneumococci and *E. coli.* If desired, both polysaccharide and protein can be derived from the same bacteria to give a stronger immunogenic effect. The toxoids of tetanus and diphtheria have been approved for human use, and tetanus toxoid was used in the examples. However, other proteins would be operative.

The reductive amination covalently couples the terminal aldehyde group of the polysaccharide to a free amino group on the protein through a

$$-CH_2-\underset{\displaystyle H}{N}-\text{protein}$$

linkage where the $-CH_2-$ derives from the aldehyde group. There is no significant cross-linking by this method and the conjugates are water-soluble to a considerable extent. A cyanoborohydride reagent may be utilized to effect this reductive amination. The amount of cyanoborohydride is not critical. Typical amounts may range from about 30 to 100% by wt. based on the

* * *

17. The conjugate of claim 16 wherein said reducing sugar moiety is N-acetylmannosaminitol.

18. The conjugate of claim 11 wherein said linkage is through a lysine amino group on the protein.

19. The conjugate of claim 11 wherein the polysaccharide and protein are derived from the same bacteria.

20. A method of immunizing against infection susceptible humans or animals comprising, administering a vaccine comprising the conjugate of claim 11 in an immunogenic amount by intramuscular or subcutaneous injection.

21. The method of claim 20 wherein the dosage of the conjugate is equivalent to from about 5 to about 25 micrograms for the human infant.

22. The method of claim 21 wherein human infants are immunized with a vaccine comprising at least one of (a) the conjugate of meningococcal polysaccharide, and (b) the conjugate of *H. influenza* polysaccharide.

23. A vaccine comprising at least one conjugate as defined in claim 11.

24. A vaccine for infants comprising the conjugate of claim 11 wherein the initial non-conjugated polysaccharide is of the type for which the immune response is non-thymus-controlled.

25. A human infant vaccine comprising the conjugate of claim 11 wherein the polysaccharide comprises at least one of meningococcal polysaccharide and *Haemophilus influenza* polysaccharide.

26. A vaccine as in claim 24 in a dosage unit form wherein the conjugate is present in the equivalent of from about 5 to about 25 micrograms based on the human infant.

* * * * *

APPENDIX B – Excerpts from trial transcripts of Northern American Vaccine, Inc. and National Research Council of Canada v. American Cyanamid Company and Praxis Biologics, Inc. (United States District Court for the Southern District of New York in 91-CV-1449) (1992)

John Diaz, Esquire Opening Statement (August 3, 1992)

[12] so when it did make antibodies to one of these highly cross-linked or significantly cross-linked conjugates, it made antibodies to these proteins but those antibodies were not effective against that was causing the infection which in this case is the polysacchride.

So this system did not work because it was too heavy, it sunk the ship, molecules came out of the solution and in addition the proteins masked the polysacchride so that the immune system could not see it and would not make effective antibodies. And that was the problem that the '170 patent addresses and that is the problem that the '170 patent solves and it solves it as you've just seen by just making polysacchride chains which have free aldehyde groups, single terminal aldehyde groups on one end or on both ends and leaves this backbone clean.

If we could put that PX 306, maybe put that on the second easel. Your Honor, if you contrast 306 to 302, the significant differences are the backbone in 306, the backbone of the patented conjugate molecules is clean as a whistle. That's significant. When that molecule is injected into the human body, human infant system, the human infant immune system sees the polysacchride, if that's Haemophilus influenza it sees that and it makes antibodies to it. If it's mening, it sees the mening and makes antibodies to it. It cannot do that with these highly

* * *

Dr. Gary Schoolnik Cross-Examination
(August 10, 1992)

[539] be read a terminal aldehyde group at each end.

Now, let me just concede something to you. If the Haemophilus influenzae polysaccharide was not mentioned in that claim, and if it were not the subject of this suit, I would be far more comfortable, perhaps, being persuaded by your argument. But for me, you know – I'm speaking only as an expert witness here, I guess – the fact that that polysaccharide is mentioned specifically in the claim, the fact that those skilled in the art as of 1981 knew its structure and knew what would happen to it upon periodate oxidation, I interpret all of this language with reference to that, and that's just, you know, how I have come to understand these words.

Q. Is it your view, Dr. Schoolnik, that because certain polysaccharides are mentioned in the claims, that based on what would happen to those polysaccharides in this periodate oxidation reaction, you have to modify this phrase accordingly, namely, that's how you find out what a terminal aldehyde group means? Is that your view?

A. My view is that since we are really talking about the Haemophilus influenzae polysaccharide, and in reference in particular to that polysaccharide and this lang uage, my view is that this language is interpretable for me – now I'm just saying for me as a scientist, I would go to the claims, and since Hib polysaccharide is what we're all

[540] talking about here, I would say how does this language read with respect to what we know about Hib or what we would have known about it as of 1981.

Now, all of the other polysaccharides that are present in that claim may or may not be relevant. But for me as a scientist, since we are talking about a specific example, I'm not that concerned about the other polysac-

charides there. I am concerned about Hib and how we would interpret this language with respect to it.

Q. But if you're interpreting this language with respect to Hib, when you look at claim 12, you also have to interpret the language with respect to the other polysaccharides that are mentioned there, isn't that right, by pure logic?

A. Well, we've made, I think, a general agreement over the last several days of testimony that one must, as a matter of principle, interpret the language with respect to each of the polysaccharides that might come under consideration. So, I mean, I suppose if this was a suit about pneumococcal vaccine, then we would spend most of our time wondering about the pneumococcal polysaccharide and how the language would pertain to it.

Q. But I'm asking you, I mean, we are not restricted to any specific word in this claim. In claim 12, is it not true that there's a group of polysaccharides which include

[541] meningococci, Haemophilus influenza, pneumococci, B-hemolytic streptococci, and E. coli? Does it include all of those?

A. Well, it does.

Q. Just yes or no. Does it include them?

A. Yes.

Q. Please restrict yourself to answering my questions.

A. Yes, it does.

Q. Now, if you are interpreting this language you just read in column 3 with respect to Haemophilus influenza, doesn't pure logic – you told me you studied logic – doesn't pure logic tell you that you also have to look to the other polysaccharides by the same token and in the same manner?

A. Well, we could go over each one of them and see. But I tell you to me, as a scientist, where I have to deal with reactions as they occur on a particular molecule, I

try to be as focused in my comments as possible.

Now, maybe that's not what a good lawyer would do, but as a scientist, I am concerned with the examples in the patent. And we've talked extensively about those, and I'm concerned about only one of that group, namely, Haemophilus influenza, because that's what's at suit.

Beyond that, you know, I would have to put on my

[542] scientist hat and reanalyze the relevance of each of the many other – you know, we have quite a few polysaccharides listed there. I would have –

THE COURT: They're all referred to. I'll tell you, you're not the lawyer, you don't have to worry about what the case is about or the issues in the case. Obviously you're a very sophisticated man. You're not coming in here and acting like a robot. You want to know the context and the purpose of your testimony, and of course you know what the case is about. But it really is not up to you to argue the case, it's to simply testify.

And every single of one of those diseases, becteria, whatever you call them, are listed in 12, and they're all relevant. Regardless of what this case is about, they're relevant to the interpretation of the patent, and that's what Mr. Dunner simply asked you.

And I think the answer is yes. If you're interpreting the patent, if you're interpreting claim 12, you have to take into account everything in claim 12, right? You do?

THE WITNESS: All right. I –

THE COURT: Of course you do.

THE WITNESS: Okay.

THE COURT: Let me just interrupt, and you can go back to your train of questions, but if you could just take

* * *

[596] THE WITNESS: That's correct.

THE COURT: Okay.

MR. DUNNER: And, your Honor, my point is merely that he keyed everything to whether it's antigenic or not.

THE COURT: No, he didn't.

THE WITNESS: Part of it is simply starting with your proposition you come out with a dirty backbone.

MR. DUNNER: Which he defined as something which was not antigenic.

THE COURT: Well, okay.

Q. Is that correct?

THE COURT: I guess there will be other things that could make things antigenic. If it was just, you know, skimmed milk it wouldn't be antigenic either.

Q. To proceed, Dr. Schoolnik, you also are of the view that, to the extent pneumococci serotypes have dirty backbones, they would not be included within these claims, correct, not be embraced by them?

A. It just seems to me that –

Q. Yes or no?

THE COURT: Please, that's sort of a yes or no question. The answer is yes, isn't it?

THE WITNESS: Yes.

Q. And that's also true of every B-hemolytic streptococci, correct, the same thing?

[597] A. Yes.

Q. The same thing is true about E. coli?

A. Yes.

Q. Well, let's just examine some of these structures. I'd like you to look at exhibit K, if you would, in your book. That is an article written by Dr. Jennings, is it not?

A. Yes.

Q. I'd like you to look at page 105 of this paper and page 106, 106 in particular.

A. All right.

Q. Toward the bottom you will see –

MR. DIAZ: Your Honor, I'm just going to offer a formal objection, technical objection on this article. The patent speaks as of the time it was filed, May 1981. He's talking about a 1990 article.

THE COURT: This article is what?

MR. DIAZ: It's a 1990 article.

THE COURT: Well, I don't know whether it bears or not. We'll just have to see.

MR. DIAZ: I just want to register a formal objection.

THE COURT: Overruled. We will take it for whatever weight it is worth. If it is not entitled to weight, I will not give it any.

* * *

Dr. Gary Schoolnik Cross-Examination
(August 11, 1992)

[766] Cynamid memorandum entitled the Jennings '170 patent describes forming a single aldehyde group at one end of a polysaccharide, that is the title of the memorandum. And it is dated August 5, 1992. So that's what my question is about.

And the question is: In light of those quotations from the patent which really do speak of a terminal or a terminally-located aldehyde through – all in the singular, and we've been through those quotations many times in the trial, I'd like to get your position as to why, in view of those, why this patent can be interpreted as covering the formation of the polysaccharide protein conjugate, and I'll use it in the best sense I can, with aldehydes at both terminal ends?

THE WITNESS: Well, my position is that although

this uses the singular, my position is that the singular refers to one end of a molecule that may have more ends, two or more ends. It's not inconsistent with a single terminal aldehyde on each of the two ends. And my reasons for that come, by and large, from the fact that within the claims, and in specific, claim 12, there are several examples, including Haemophilus influenza, which if one practiced the art and one knew, and having knowledge of the structures of these polysaccharides as of 1981, one would anticipate the production of aldehydes at both ends as well as in some

[767] cases one end.

So my entire interpretation of the language where it is singular is driven by the specific examples of polysaccharides in claim 12, which because of their structural properties, when subjected to oxidation, would yield a polysaccharide molecule with an aldehyde at both ends. So that for me is the most compelling reason, okay.

THE COURT: Now, I would also – I don't know whether – maybe this is not feasible for you, but, again, taking advantage of your presence here, I want to ask you something and it relates to a memorandum filed by Cynamid today, and you would have no reason to have read this, but I have.

Now, let me ask you this, are you now familiar with what I think the lawyers have called the prior art, and what I assume that to mean is that the experimentation, the developments, the successes, the failures of this field of technology prior to the Jennings patent?

THE WITNESS: I believe I am.

THE COURT: All right, now. Would you take – I should have given this to you before the recess, but we can just sit here for a minute now. Would you read the portion of this memorandum at the bottom of page 2

underneath the heading which starts with, Dr. Jennings's role, and would you read it going over to – read that paragraph. Now, the

* * *

Dr. Harold J. Jennings Direct-Examination
(August 17, 1992)

[957]won't bother getting it out because there is no dispute about that.

Did you testify in deposition in words or substance that you gave your 1980 article, PX-168, to your patent attorney and he used that article as a basis for drafting your patent application.

A. Yes.

THE COURT: Is this '80 or '81?

MR. DIAZ: It's the '81 article.

THE COURT: Was this based on an '80 talk?

MR. DIAZ: Based upon the '80 talk, you Honor.

Let me see if I can clarify the record.

Q. The '81 article, Exhibit 168, is kind of a summation or, it has in substance what you presented orally at the 1980 NIH symposium, is that correct?

A. It's practically identical, and I gave the patent attorney the draft of the 1981 paper, the experimental part, to write the patent.

Q. So PX-168 had not been published and you gave him a draft of that publication?

A. Yes, I did.

Q. Would you please turn to Plaintiff's Exhibit 168, page 1016. And about right-hand column, about lines 15 to 17. Do you see that, where you state – why don't you read that beginning with "The ideal situation."

* * *

[965]THE COURT: Look, I'm not criticizing, you have a right to read and you generally don't read, but anyway, if you read, just go a little slower, because I'm trying to make notes.

MR. DIAZ: You're right, I would prefer not to read. With the Court's indulgence, I will try not to read.

Q. I'm talking about your 1981 and 1982 articles, I've read them, you've read them.

And when I read them, they talk about experiments which are carried out on specific polysaccharides, and the specific polysaccharides in those articles are mening A, mening B, and mening C, correct?

A. Correct.

THE COURT: Just a minute.

(Pause)

THE COURT: Go ahead.

Q. When you gave your 1981 article in manuscript form to your patent attorney, did you tell your patent attorney that he should restrict the application in your invention to mening A, B, and C?

A. No.

Q. Did you discuss with your patent attorney whether your conjugates should be restricted to conjugates in which the polysaccharide component was mening A, mening B, and/or mening C?

[966]A. I discussed with the patent attorney the general applicability of the method to other important polysaccharides, and I believe these other important polysaccharides are mentioned in the patent. They are Haemophilus influenza, streptococcus pneumonia, group B streptococcus, and Escherichia coli.

Q. Did your patent attorney agree with you or disagree with you when you told him you wanted to include these other polysaccharides?

A. He was very positive about including these.

Q. And did he include these other polysaccharides?

A. Yes, he did.

Q. So that when you wrote your patent application, you considered your invention to be broader than the specific experiments you had carried out as of that date, i.e., experiments with mening A, mening B and mening C, right?

A. Yes, I did.

Q. And you put that into your patent application, did you not?

A. I did.

Q. Would you look please at the patent which is in your book as PX-10; and I'm directing your attention to column 3, line 18-20.

Are the polysaccharides which you've just

* * *

[984]Would you mark that mening C?

A. Yes (complying).

Q. Thank you.

(Witness resumed the stand)

Q. Now, Doctor Jennings, it is defendants' contention in this case that in the experiment on Group C reported in Columns 5 and 6 of your patent, you intentionally selected starting materials and conditions so as to achieve a monofunctional Group C polysaccharide chain. Is that contention correct?

A. That's not correct.

Q. When you started off planning your Group C experiment, what result did you expect to achieve?

A. Well, I suppose, in effect, we would be willing to accept any result, as long as we could get terminal aldehydes. I mean, we didn't really care.

Q. Right.

A. And in actual fact, what we got, in essence, was an aldehyde at one end.

Q. And did you expect to get an aldehyde at both ends?

A. We would have anticipated that we would, yes.

Q. And that anticipation was based upon your 1975 work with mening C; is that correct?

A. Yes.

* * *

[1000] about 2,000."

Q. My specific question is: In the terminology you use there "linkage to a terminal portion of the polysaccharide," by that statement did you intend that the linkage of protein had to be to only one terminal portion of the polysaccharide?

A. No, we did not.

Q. Would you look, please, at claim 11, and it's up on the board here, where that same language is used, "linkage to a terminal portion of the polysaccharide." Do you see that?

By that language, did you intend that the linkage had to be to one terminal portion of the polysaccharide?

A. No.

Q. Did you intend in that language to be broad enough to include linkage to both ends of the polysaccharide?

A. What we intended it to be, also to cover the aldehyde at each end, and this can be read from the difference between my publications and also the abstract — sorry, the patent, in which we do allow for cross-linking.

Now, to get cross-linking, we would have to have at least two aldehydes on one polysaccharide molecule.

Q. To get some cross-linking you would have to have two aldehydes, one on each end?

* * *

Dr. Harold J. Jennings Cross-Examination (August 17, 1992)

[1107] Q. And you could have done it and you didn't do it?

A. That's correct.

Q. And the results of your consultation with Connaught, no product according to the Jennings method, right?

A. According to my method, they did make a product.

Q. What product did they make?

A. They sent me details of a conjugate that they made and I looked at the results that they got and I wrote back to them and told them how to make this a better type of conjugate.

Q. They sent you an experimental batch of conjugate that they had made according to your procedure, meningococcal conjugate, right?

A. But they also sent me the written work that describes this conjugate.

Q. With regard to the meningococcal conjugate, correct?

A. That's correct.

Q. And you got it and you reviewed it and you talked to them about it some more, right?

A. That's correct.

Q. And what I'm saying is when all is said and done, they never took that, they never developed it they never tried to license it and they never marketed it in the United

[1108] States or anywhere, correct?

A. That's correct.

Q. And the fact of the matter is that Connaught does make a conjugate vaccine, don't they?

A. Yes, they do.

Q. They make a conjugate vaccine against Hib, correct?

A. That's correct.

Q. And they do not use the Jennings method?

A. That's correct.

Q. Indeed they use the Robbins and Schneerson method, correct?

A. I think they use a derivation of it, but not exactly the Robbins and Schneerson method.

Q. Well, if you looked at the package insert, you would see the footnotes of Robbins and Schneerson up front?

A. That's true, basically.

Q. The basic underlying principle for the Connaught vaccine was Robbins and Schneerson?

A. That's correct.

Q. And they make it and it works in two-, four- and six-month olds.

A. That's not correct.

Q. It doesn't work in two-, four- and six-month olds?

[1109] A. Not the first vaccine that they made, no.

Q. Well, they make one today that works in two-, four-, and six-month olds?

A. I'm sorry, I'm confused by – I thought you were talking about the first one that they made.

Q. Let's talk about today. Connaught makes a Hib vaccine, it's a conjugate vaccine and it works, correct?

A. This is the one that is supplied through the Institute Mirieux. I've heard of it, I've heard that they're doing it.

Q. You're a man in this field, are you interested when somebody succeeds in putting on together a conjugate vaccine that you've been working on for over a decade?

A. Yes, I am interested.

Q. That captures your attention?

A. Yes. But, on the other hand, I do not know the exact procedure that they're using now because I have no relationship with Connaught anymore.

Q. I understand, but you are aware and you know

that they use a derivation of the Schneerson and Robbins method to make a Hib vaccine and that vaccine works in infants, doesn't it?

A. Yes, it does.

Q. There is absolutely no proof that the Jennings method, when applied to any polysaccharide, can yield a

* * *

[1134] Q. And that describes the conjugates that you had actually made in your lab, right?

A. That's correct.

THE COURT: What exhibit is this?

MR. THOMASCH: This is Plaintiff's Exhibit 168, your Honor.

THE COURT: That's the '81 article?

MR. THOMASCH: The '81 article given to Mr. Thomson.

Q. Regardless of the similarities or differences between this article and the patent, the experimental work which underlies this article is the very same experiments that are reported on in the patent, correct?

A. That's correct.

Q. All right. Now I'd like to take a look at your language in this article that you drafted, and start at page 1012. The article begins, "Despite the demonstrated success of the groups A and C capsular polysaccharides of Neisseria meningitidis in providing homologous serogroup immunity in humans, there still remain major problems associated with their use as human vaccines."

That is verbatim the same introduction that you gave to the NIH, correct?

A. Yes.

Q. And what you are saying here is that the capsular

* * *

Dr. Ronald John Eby Direct-Examination
(August 19, 1992)

[1323] A. Approximately a third of the articles and all the of the abstracts.

Q. Dr. Eby, I want to go back in time. When did you start working for Praxis?

A. I started in October of 1983.

Q. What was your initial position?

A. I was hired as a research scientist.

Q. What were your initial responsibilities as a research scientist?

A. I was hired to develop the Haemophilus B conjugate vaccine for Praxis.

Q. Could you slow down again?

A. Yes, I could.

Q. When you started working for Praxis, where did you work specifically?

A. Initially, I worked in the laboratory of Porter Anderson at the University of Rochester.

Q. Did Praxis have laboratory space available for you in its facilities at the time?

A. Not at that time. They were undergoing construction of those facilities.

Q. Approximately what number hire were you at Praxis? How many people we are employed by Praxis before you got there?

A. I was approximately number six in the employees.

[1324] Q. Through what period of time did you work in Dr. Anderson's laboratory?

A. Approximately from October of 1983 through January of 1984.

Q. When did you first meet Dr. Anderson?

A. I met Dr. Anderson in a job interview in August of 1983.

THE COURT: You worked for Anderson at Praxis, right?

THE WITNESS: I worked with Dr. Anderson.

THE COURT: At Praxis?

THE WITNESS: Yes. Praxis at that time existed at 300 East River Road, but there was no lab facilities available, so for the interim I was using the facilities at the University of Rochester.

Q. You mentioned that during a job interview you talked with Dr. Anderson. During that job interview, did you discuss polysaccharide protein conjugates?

A. Yes. We have discussed the work that Dr. Anderson had performed on preparing oligosaccharide Haemophilus conjugates, link to proteins. His work on use of the acid hydrolysis and reductive amination of those oligosaccharides to the protein.

We discussed their immunogenicity in terms of both animals and humans, and we continued to discuss other

[1325] of preparing conjugate vaccines of Haemophilus, and, in particular, we discussed the use of periodate oxidation to generate fragments and to couple those fragments to proteins to make conjugate vaccines.

Q. During the job interview while you were talking with Dr. Anderson, did you discuss any advantages of periodate cleavage approach?

A. Yes. We looked at the chemistry, we looked at the structure of the Haemophilus polysaccharide, determined where cleavage sites would occur in the polysaccharide that reaction of those vicinal hydroxyl groups in the molecule would lead to the formation of fragments, that these fragments would indeed have aldehydes at both ends of the fragments, that we could control the reaction by the amount of periodate used in the reaction and the oxidation step.

We discussed the difference that these fragments would have free aldehydes over what he had currently been

using in the acid hydrolysis step, and that there would be a difference in reactivity of these aldehydes which would lead to an increase yield in the reaction.

We also discussed a little bit of the possible type of conjugates that we would form, that we would have fragments which would have two aldehydes, and therefore, we would have the potential of crosslinking occurring in the conjugates.

[1326] Q. When you were hired by Praxis, what was your understanding of the first work that you would be doing for Praxis?

A. Well, based on the extensive job interview, it was my idea that I would be working on the formation of the Haemophilus B conjugate vaccine using the periodate approach.

Q. Was that what actually happened?

A. Yes, it was.

Q. When you started working for Praxis, what was your understanding of the general business plan of Praxis?

A. Well, the general business plan was to first commercialize the polysaccharide vaccine to develop the manufacturing capability, to sell that product which would be the polysaccharide vaccine.

Q. When you speak of the term polysaccharide vaccine, are you speaking of the polysaccharide from Hib as its purified from the bacteria?

A. Yes.

Q. It was not a conjugate vaccine?

A. That's right. The initial products Praxis had envisioned was the Haemophilus polysaccharide for Haemophilus B disease, and that was our primary goal. We would use the sale of the polysaccharide vaccine to generate revenue that would continue to drive the research of the

* * *

[1336] age, infants?

A. Approximately one year later we had an approval for 15 months and older.

Q. Did Praxis ultimately get approval for infants at two, four, and six months, for its HibTITER vaccine?

A. After the successful completion of an efficacy trial in northern California, which indicated that the vaccine had a 100 percent efficacy in the young infant, we were granted a license for the infant indication. I believe that was in October of 1990.

Q. Dr. Eby, what competitors of Lederle Praxis sell vaccines for Hib in the United States?

A. There are two competitors. One is Merck and the other is Merieux Connaught.

Q. With respect to Merieux Connaught, what is the name and type of the vaccine that they sell?

A. They sell Haemophilus B conjugate vaccine called Prohibit which basically is a vaccine prepared by the method of Schneerson and Robbins.

Q. For what age groups is Prohibit approved?

A. Currently Prohibit is approved for infants 15 months and older.

Q. That's in the United States?

A. That's in the United States.

Q. Is Prohibit approved for infants anywhere in the

* * *

[1338] months of age.

Q. What is the market share tha the Merck product has in the market for Hib vaccines in the U.S.?

A. Currently, the Merck product occupies about 5 percent of the market.

Q. Does that mean that HibTITER has about 88 percent of the market for Hib vaccines in the U.S. today?

A. That's correct.

Q. How long has HibTITER had such a large market share?

A. The product was granted an infant license in 1990 and we got about that market share several months, one or two months, after that licensure.

Q. Are you aware of any reports dealing with the incidence of meningitis caused by Hib since HibTITER started being marketed?

A. Yes, I am.

Q. What do those reports conclude?

A. Those reports conclude that there has been a marked decease in the incidence of Haemophilus disease after licensure of the conjugate vaccines in infants.

Q. Is that decrease due to the sales of HibTITER?

A. Primarily due to the sales of HibTITER, since we currently have about 88 percent of the market.

Q. Dr. Eby, we'll be putting up on the easel a copy

* * *

[1344] native polysaccharide, that we have shown at the top of this exhibit, that the periodate cleavage could occur anytime, or any location where there is vicinal hydroxyls which occurs repeatedly along the length of the polysaccharide chain?

A. Exactly. Again, we're not confined to just where the yellow arrows are, but anyplace we have vicinal hydroxyl groups, anywhere along the polysaccharide chain, you can get cleavage with periodate.

Q. The brackets show with subscripts various numbers, 20, 40, 10 and 30. Does that denote that within the brackets there would be various numbers of repeating units?

A. Yes, this is just a shorthand way of saying that these repeating units within this bracket are repeated 20 times, that the repeating units inside this bracket are

repeated 40 times. It's just a random way of showing that this is a very long molecule and instead of taking up the whole courtroom, we've reduced it down to a poster size board in which we have fragments or brackets with different sizes in polysaccharide.

Q. Would you now describe what happens when you treat the starting Hib polysaccharide with periodate in the process for making HibTITER?

A. When the Haemophilus B polysaccharide in the native state is treated with periodate which is denoted by

[1345] the IO4 minus, that is the periodate ion, there undergoes a random cleavage in the backbone between the vicinal hydroxyl groups of the ribotol unit to give you fragments of random molecular size with aldehyde functions at each end of the fragment. So there is cleavage between the vicinal hydroxyl groups and for formation of aldehyde groups at each end of the fragment. And what is denoted in the schematic is that we can generate fragments having aldehydes at both ends but also fragments of various sizes so that we can get a random mixture of fragments, sizes anywhere from very small to very large, all of which will have aldehyde groups at both ends of the molecule.

(Continued on next page)

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[1348] Q. Would you describe what's illustrated on exhibit XH?

A. On exhibit XH is a schematic of the overall production of the Haemophilus B conjugate vaccine known as HibTITER from the starting polysaccharide all the way through the conjugation reaction.

What we saw in the previous exhibit was basically

the top portion of this schematic in which now the polysaccharide is denoted by this long wavy line on the left-hand side of the schematic. We removed all of the chemistry, essentially, that we saw in the previous exhibit.

That polysaccharide undergoes a random oxidative cleavage with periodate to generate smaller fragments having aldehydes at both ends of the fragments. These fragments, as we pointed out before, are sized to a narrow-size distribution, not shown in this particular schematic.

These fragments are then coupled to a protein denoted by the circle in the diagram, and in particular, in Hib-TITER, this protein is CRM 197. The protein is coupled to the fragments by a process called reductive amination in which the aldehyde groups are reacted with the amino groups on the protein to give us a conjugate vaccine, denoted in the bottom row of the schematic.

Q. You mentioned that the protein was CRM 197?

A. Uh-huh.

* * *

[1351] appears to be attached in two different ways, one at one end and one polysaccharide is attached at both ends to the same protein. What do you call that when the polysaccharide is attached at both ends to the same protein?

A. Again, because we are using fragments which have aldehydes at both ends, both ends of the molecule are reactive. They can attach themselves to one side to the protein and what we call a loop and attach themselves to the other side of a protein molecule. So this formation where the fragment is linked at both ends to the same protein molecule, this is called a loop structure.

Q. Would you also point out on the exhibit the existence of crosslinking?

A. Okay. Crosslinking occurs when you have structures higher than monomer, in other words, dimers, trimers, any fragments that may even be higher than that. That occurs when the saccharide binds at one end to one protein molecule and the other end binds to another protein molecule, not the same protein.

So if the fragment binds to the same protein molecule, you get a loop; if it binds to two different protein molecules, you get a crosslink between them.

Q. Dr. Eby, what is the estimated molecular weight of a typical monomer structure in HibTITER?

A. Typically, the protein is approximately 60,000.

* * *

Dr. Ronald John Eby
Cross-Examination (August 20, 1992)

[1447] simply referring to different parts of the patent about which I had heard many times.

And so I will say right now that on the question of interpretation, his opinion on interpretation, I really will disregard that testimony. Not any disrespect to you, but we had those objections and it was repetitious anyway, and so you do not need to cross-examine him about that and try to undermine his opinion about interpretation because he really didn't give anything very much.

Let's move on.

MR. DIAZ: Okay, I understand the Court will not rely upon that testimony in interpreting the patent.

THE COURT: Yes, right.

MR. DIAZ: Thank you very much, your Honor.

Q. At pages 23 and 24, defendants' pretrial memorandum –

THE COURT: All right, now let me get that.

(Continued on the next page)

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APPENDIX C – Excerpt from Brief of Plaintiffs-Appellants North American Vaccine, Inc. and National Research Council of Canada filed at the United States Court of Appeals for the Federal Circuit on January 15, 1993

Claim construction is an issue of law freely reviewable on appeal. *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1177, 20 USPQ2d 1094, 1097 (Fed. Cir. 1991); *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 986, 6 USPQ2d 1601, 1604 (Fed. Cir. 1988); *Intervet America, Inc. v. Kee-Vet Laboratories, Inc.*, 887 F.2d 1050, 1053, 12 USPQ2d 1474, 1476 (Fed. Cir. 1989).

Here, the claim language and the specification require a construction of the claims to embrace *Haemophilus influenza* polysaccharides with a protein linkage to both terminal portions. The claims expressly recite *Haemophilus influenza* polysaccharides and the specification expressly teaches the use of *Haemophilus influenza* polysaccharides in the invention. Since *Haemophilus influenza* polysaccharides are the only polysaccharides present in Cyanamid's HibTITER product and they include a protein linkage to both terminal portions, infringement follows as a matter of law.

A. The Claim Language "*Haemophilus Influenza*" Requires That The Claims Be Interpreted To Include, Not Exclude, *Haemophilus Influenza* Polysaccharides With A Protein Linkage To Both Terminal Portions

"Claim interpretation must begin with the language of the claim itself." *Stiftung*, 945 F.2d at 1177, 20 USPQ2d at 1098. The express recitation of *Haemophilus influenza* in the claims requires that "a terminal portion" be

APPENDIX D – Excerpt from Reply Brief from Plaintiffs-Appellants North American Vaccine, Inc. and National Research Council of Canada filed at the United States Court of Appeals for the Federal Circuit on April 15, 1993

ARGUMENT

I. THE DISTRICT COURT'S JUDGMENT OF NONINFRINGEMENT SHOULD BE REVERSED AS A MATTER OF LAW.

Contrary to the impression that Cyanamid seeks to create with its brief, NRC's position in this appeal calling for reversal of the district court's judgment of noninfringement raises only questions of law and does not involve disturbing any of the district court's underlying factual determinations.

The first step in the infringement analysis is claim interpretation which is a question of law as shown in NRC's main brief and as developed further in this reply brief. The second step in the infringement analysis, application of the properly interpreted claims to the accused product, involves no factual issues in this case because the composition of the accused HibTITER product is undisputed.

A. Cyanamid Cannot Defend The District Court's "Monofunctional" Claim Construction Which Erroneously Excluded "Difunctional" *Haemophilus Influenza* Polysaccharides From The Claims

Cyanamid's attempt to posture the appeal as involving fact issues, subject to the clearly erroneous standard of review, cannot withstand analysis. At the heart of this

appeal is the district court's construction of asserted claims 12 and 25 as limited to what it called "mono-functionality," *i.e.*, protein linkage to *only*

APPENDIX E – Excerpt from transcript of Oral Argument at the United States Court of Appeals for the Federal Circuit on July 12, 1993

Judge: There at least two hotly contested terms as I have heard the argument this morning . . .

Smith: Right . . .

Judge: And you've just given me . . .

Smith: If you take that claim language, and it's the interplay between that claim language and the recitation of Haemophilus influenza in the claim which has the linkage to both ends, and the interplay between all those factors adds up to the ball of wax that is called claim construction, that is the province of this court to review de novo. We are not contesting any of the District Court's findings about any of those terms, we are flowing with that, the question before this Court is one of claim construction that should be reviewed de novo, Your Honor.

Judge: Thank you, Mr. Smith.

Smith: Thank you very much.

Judge: Case is submitted.